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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 29

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Appellant(s): Samuel Bogoch

Judith L. Toffenetti
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed October 5, 1995.

(1) *Status of claims.*

The statement of the status of claims contained in the brief is correct.

(2) *Status of Amendments After Final.*

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(3) *Summary of invention.*

The summary of invention contained in the brief is correct.

(4) *Issues.*

The appellant's statement of the issues in the brief is correct.

(5) *Grouping of claims.*

The brief includes a statement that claims 1 and 2 do not stand or fall together but fails to present reasons in support thereof. Therefore, these claims are presumed to stand or fall together.

(6) *Claims appealed.*

The copy of the appealed claims contained in the Appendix to the brief is correct.

(7) *Prior Art of record.*

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

Bogoch, E.S. "Elevated Levels of Anti-Malignin Antibody are Quantitatively Related to Longer Survival in Cancer Patients." Protides of Biological Fluids, vol 31, (1984), pp. 739-747.

Bogoch, S. "Malignin, Anti-Malignin Antibody and Scantag." Protides of Biological Fluids, vol 30, (1983), pp. 337-352.

Zar, J.H. *Biostatistical Analysis*, 2nd edition, Prentice-Hall, Inc., Englewood Cliffs, NJ, 1984, p 278.

Stevenson, F.K. "Tumor Vaccines." FASEB Journal, vol. 5, no. 9, (June 1991), pp. 2250-2257.

(8) *New prior art.*

No new prior art has been applied in this examiner's answer.

(9) *Grounds of rejection.*

The following ground(s) of rejection are applicable to the appealed claims.

It is noted that while the prior art of record (See rejection under 35 U.S.C. § 103 on page 5 of the Office Action dated 9/12/94, and also Bogoch et al listed above) may suggest the use of Recognin or malignin in the treatment of cancer, the rejection under 35 U.S.C. § 103 was withdrawn in the Advisory Action dated February 22, 1995, and the rejection under 35 U.S.C. § 112, first paragraph was maintained because the one of ordinary skill in the art would not have a reasonable expectation of success in treating cancer using the claimed compositions and methods for the reasons which follow.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. The specification teaches that Recognin is present in several cell types of malignancy by immunostaining using anti-Recognin antibodies (p 7). The specification also teaches that anti-Recognin antibodies inhibit the growth of small lung carcinoma cells *in vitro* (p 12-13). The specification discloses that levels of anti-Recognin antibody in humans increase with age and are increased in patients with breast cancer (p 15). The specification does not teach that Recognin, when administered as a vaccine, prevents or treats clinical cancer. Because patients diagnosed with cancer already have increased serum levels of anti-Recognin antibodies, as disclosed in the specification, it is not predictable whether enhancing these antibody levels by administering a Recognin vaccine would be effective in treating the cancer. In addition, Stevenson discloses that vaccination against cancer poses other problems such as the selection of a suitable adjuvant for use in humans which would result in a sufficient antibody titer (p 2256, column 1). Because it is unpredictable whether the administration of Recognin would result in the production of antibodies capable of preventing or treating clinical cancer, it would require undue experimentation to determine how to use the claimed composition and methods for the treatment of cancer.

Claims 1 and 2 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

(10) *New ground of rejection.*

Claim 2 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The meaning of the phrase "immunological specificity" in claim 2 is vague. It is not clear what properties characterize "immunological specificity". For example, it is not clear whether this phrase means that the vaccine product is cross-reactive with antibodies which recognize Recognin (as in claim 1) or whether the vaccine product may have other effects on cells of the immune system which may be specific to malignin, Recognin L or Recognin M.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. The specification discloses Recognin M as being produced from MCF7 breast cancer

cells and Recognin L as being from P3J lymphoma (p 6). The specification teaches that malignin is the immunogenic fragment of the Recognin precursor protein (last paragraph on page 5). The specification also refers to anti-Recognin and anti-malignin antibodies interchangeably (see page 14, line 2 for example). It appears from the specification that Recognin L, Recognin M, and malignin all react with the same anti-malignin/anti-Recognin antibody. It also appears that the term malignin and Recognin are used interchangeably. The specification does not disclose other Recognins. In the absence of evidence to the contrary, it would require undue experimentation to identify other Recognins and to determine whether these other Recognins would be effective to inhibit or destroy cancer cells upon administration as a vaccine because the properties and specificity of the antibodies generated by the other Recognins is unknown. If the specificity of the antibodies generated by other Recognins is identical to Recognin L, Recognin M, and malignin, it is maintained that it is unpredictable whether administering a Recognin vaccine would be effective in treating the cancer because cancer patients already have increased serum levels of anti-Recognin antibodies, and it is not predictable whether enhancing these antibody levels would be effective in treating the cancer.

The specification states that the Recognin derivative vaccine can be a malignin glycoprotein precursor which has a molecular weight of 250,000 daltons (p 17). The specification teaches that malignin has a molecular weight of about 10,000 daltons (p 5). The specification does not teach how to make other derivatives of Recognin which produce anti-Recognin antibody. It is unpredictable whether the antibodies produced upon administration of

a much larger 250,000 dalton precursor protein would be the same as those produced upon the administration of a 10,000 dalton protein because the conformational epitopes of the two glycoproteins would not necessarily be the same due to differences in the three dimensional structure of the glycoproteins. Therefore, antibodies produced upon administration of a large precursor Recognin derivative vaccine may have different specificities than antibodies produced when the 10,000 dalton protein Recognin is administered. It is also unpredictable whether the conformation of the epitopes of the Recognin glycoprotein would be maintained in derivatives with additional chemical groups attached to Recognin because the three dimensional structure of these derivatives would be different than the native glycoprotein. Due to the unpredictability concerning the specificity of the antibodies generated by Recognin derivatives, it would require undue experimentation to determine how to make vaccine products or derivatives of Recognin which would contain the immunological specificity of malignin, Recognin L, or Recognin M. For the reasons discussed above, it would also be unpredictable which derivatives of Recognin or other Recognins would be effective in the treatment of cancer and therefore would require undue experimentation to determine how to make and use these derivatives or other Recognins for the treatment of cancer.

Claims 1-2 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

(11) *Response to argument.*

Appellant presents three main arguments which are addressed as follows:

1) Timing and Dosage of Administration and Production of the Vaccine

On page 5, Appellant argues that the dosage and timing of the administration are taught by the specification and that clinical determinations may be utilized to determine the appropriate treatment regimen and that one of ordinary skill in the art need only follow the steps provided in the specification. Appellant argues, on page 6, that for the composition claim the specification discloses that the antigenic peptide vaccine may be produced synthetically or by cell or tissue purification procedures. Appellant states that further details concerning the art known method of synthesizing or purifying the peptide vaccine are provided in Appellant's co-pending Application Ser. No. 07/744,649 which was incorporated into the present specification by reference and therefore the specification provides an enabling disclosure for making and using the claimed vaccine.

It is maintained that providing a dosage and timing of administration is not sufficient to demonstrate that the administration will result in the inhibition or destruction of clinical cancer as claimed because patients with cancer already have increased serum levels of anti-Recognin antibodies, as disclosed on page 14 of the specification, and it is not predictable whether enhancing these antibody levels by administering a Recognin vaccine would be effective in treating the cancer. In addition, while page 17 of the specification incorporates S.N. 07/744,649 and several other Applications by reference, the incorporation of these Applications was objected

to as improper on page 2 of the Office Action dated 12/22/93 because the methods are considered essential material and essential material may not be incorporated by reference to non-patent publications.

2) Actuarial Data

Appellant argues that The Examiner has provided no evidence to support the doubts of the objective truth of the disclosure. However, it is maintained that evidence and reasons as to why it is unpredictable whether the administration of Recognin would result in the treatment of cancer has been provided in each response. A review article on tumor vaccines was cited on page 4 of the Office Action dated 11/22/93 and an excerpt from a statistics book and one of the Inventor's publications was cited in the Advisory Action dated 4/18/95. These issues are again discussed in the following response to Appellant's arguments.

Appellant states on page 7 that they provided data that demonstrate that anti-Recognin antibody levels increase in an individual harboring a tumor but is reduced upon surgical removal of the tumor. Appellant states that the actuarial data correlates the serum level of anti-Recognin antibody with the length of survival of clinically diagnosed cancer patients.

The actuarial data and Appellant's arguments have been considered but are not deemed to be persuasive. The statistical significance of the survival studies shows that there is a correlation between anti-Recognin antibodies and survival. However, it is not clear whether the antibodies themselves are capable of treating or preventing cancer or whether other factors may

be involved. This argument is supported by Zar (p 278 of *Biostatistical Analysis*) who states the following:

> "Although we have assumed a mathematical dependence of *Y* on *X*, we must not automatically assume that there is a biological cause and effect relationships. Causal relationships are concluded only with some insight into the natural phenomenon being investigated and may not be declared by statistical testing alone. Indeed, it is often necessary to determine the interrlationships between the two variables under study and other variables, for an observed dependence may, in fact be due to the influence of one or more additional variables."

In addition, in the Inventor's publication of the actuarial data (Bogoch et al, Protides Biol Fluids 31:739-747, 1984) it was stated that "However, it does not necessarily follow that because an antibody *in situ* is shown to be related to survival that replacement or increase of the concentration of that antibody by means of either classical methods or either active or passive immunotherapy will be clinically effective against cancer" (p 746).

Appellant states on pages 7 and 8 that the Zar reference above bolsters their position concerning the actuarial data. Appellant cites the following quote in the third paragraph of Zar: "Equations may inaccurately represent natural process yet may be employed advantageously to predict the value of one variable given the value of an association variable". Appellant argues that even if the actuarial data does not demonstrate a direct relationship between anti-Recognin antibody level and long term survival to cancer, it is an indicator of a role for anti-Recognin antibody in defending against malignancies.

The quotation cited from the first paragraph of Zar on page 278 by the Examiner and the quotation cited from the third paragraph of Zar on p 278 by Appellant deal with two totally different issues. The first two paragraphs of Zar on page 278 relate to the **causal relationships** between variables, that is the ability of one variable to cause the effect of the other variable. While the value of one variable may correlate with the value of another variable, it does not mean that the first variable **causes the effect** of the second variable. In the instant case, although patients with increased survival have increased anti-Recognin serum antibodies, this does not mean that the increased anti-Recognin serum antibodies **caused** or are responsible for the **effect** of increased patient survival. The third paragraph on p 278 of Zar, from which Appellant has quoted above, relates to the ability to predict the value of one variable given the value of another variable if the two variables are mathematically correlated. In the instant case, while it is not known whether increased anti-Recognin antibodies cause increased survival, patients with higher levels of anti-Recognin antibodies survive longer. If this is a direct mathematical relationship, then if one were to measure the level of antibodies in a number of patients, one could predict which patients would survive longer based on the increased antibody levels. The quotation by Appellant above refers to the **prediction of the value of one variable based on the value of another variable** and does not refer to the **cause and effect** of the two variables. Therefore, as stated by Zar above, it is necessary to determine the interrelationships between the two variables before concluding that one causes the other because the observed dependence may be due to the influence of additional variables. Due to the complicated nature of the immune response in a

cancer patient, it cannot be determined that increased anti-Recognin antibodies are responsible for the increased survival without taking other variables into account.

3) *In vivo* and *In vitro* Data

Appellant argues on page 8 that *in vivo* data obtained from the use of an art accepted animal model of cancer has been presented which demonstrates the ability of anti-Recognin antibody to bind preferentially to malignant cells present in mouse brain when antibodies are administered intravenously and cites Bogoch et al, Protides of Biological Fluids, 30:337-352 (1983). Appellant argues that *in vitro* data showing the inhibition of the growth of small cell lung carcinoma cells by anti-Recognin antibody and the cytotoxicity of anti-Recognin antibody to various malignant cells is provided in the specification.

It is noted that the *in vivo* data described above has not been presented in any of Appellant's previous responses. The cited article by Bogoch et al has been reviewed but does not contain the data discussed above regarding the animal model or the administration of anti-Recognin antibodies. The cited article by Bogoch measures anti-malignin antibody in patient serum and the binding of anti-malignin antibody to cancer cells. While the administration of anti-Recognin antibodies to rats was mentioned on page 9 of the specification, this statement is not sufficient to establish the administration of anti-Recognin antibodies to rats as a model for the administration of the Recognin antigen to humans several reasons. First, a different composition was administered to the rats than the claimed composition (i.e. antibodies rather than the

antigen). Second, because the administration of the anti-Recognin antibodies does not require the generation of an antibody-producing immune response the rat experiments cannot be considered a model for the claimed method of treatment. Third, there is no indication that the binding of anti-Recognin antibodies to tumors in the brains of rats following the administration of the antibodies correlates to protection in humans following the administration of Recognin. In order for an animal model to be predictive of an effect such as the treatment of cancer, the effect must be measured and there must be some correlation of this response to the response in humans. Because the rat experiments mentioned in the specification did not involve the administration of Recognin, as claimed, and did not measure destruction or inhibition of the growth of the cancer cells, it is maintained that this model is not an art acceptable model for the claimed method of the treatment of cancer.

Regarding the *in vitro* data above, while the specification demonstrates that many types of cancer cells bind anti-malignin antibody, the cytotoxicity of the antibody is only demonstrated visually in glioblastoma brain cancer cells (page 8 and Figure 1). Similarly, the inhibition of growth by anti-Recognin antibody is only demonstrated on small cell lung carcinoma cells. It is maintained that these *in vitro* studies are not sufficient to demonstrate that the administration of Recognin would result in the treatment of cancer because the cytotoxicity measured *in vitro* cannot be extrapolated to the treatment of tumors *in vivo* where other cytokines and cell types which function in the immune response are present. In addition, other factors such as the

anatomical location of the tumor, the tumor mass, and the long tumor-host relationship make the *in vivo* system much more complex and unpredictable.

In conclusion, the sum of the data presented in response to the rejection under 35 U.S.C. § 112, first paragraph is not sufficient to demonstrate that the administration of Recognin or malignin will result in the treatment of cancer for the reasons set forth above.

(12) *Period of response to new ground of rejection.*

In view of the new ground of rejection, appellant is given a period of TWO MONTHS from the mailing date of this examiner's answer within which to file a reply to any new ground of rejection. Such reply may include any amendment or material appropriate to the new ground of rejection. Prosecution otherwise remains closed. Failure to respond to the new ground of rejection will result in dismissal of the appeal of the claims so rejected.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

JKS
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December 14, 1995

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